IN THE SPECIFICATION

On page 2, please amend the paragraphs beginning at line 25 as follows:

In one embodiment, a CARK nucleic acid molecule of the invention is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or more identical to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ ID NO:1 or 3 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a complement thereof.

In one embodiment, a CARK nucleic acid molecule of the invention is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 82%, 85%, 90%, 95%, 98%, or more identical to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ ID NO:7 or 9 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a complement thereof.

On page 3, please amend the paragraphs beginning at line 15 as follows:

In another embodiment, a CARK nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence sufficiently homologous to the amino acid sequence of SEQ ID NO:2 or 8, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In a preferred embodiment, a CARK nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to the entire length of the amino acid sequence of SEQ ID NO:2, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In another preferred embodiment, a CARK nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the entire length of the amino acid sequence of SEQ ID NO:8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]].

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of human CARK. In yet another preferred embodiment, the nucleic acid molecule

includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO:2, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In yet another preferred embodiment, the nucleic acid molecule is at least 350, 467, 762, 918, 1236, or 1275 nucleotides in length. In a further preferred embodiment, the nucleic acid molecule is at least 350, 467, 762, 918, 1236, or 1275 nucleotides in length and encodes a protein having a CARK activity (as described herein).

On page 4, please amend the paragraphs beginning at line 1 as follows:

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of rat CARK. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO:8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In yet another preferred embodiment, the nucleic acid molecule is at least 2962 nucleotides in length. In a further preferred embodiment, the nucleic acid molecule is at least 2962 nucleotides in length and encodes a protein having a CARK activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably CARK nucleic acid molecules, which specifically detect CARK nucleic acid molecules relative to nucleic acid molecules encoding non-CARK proteins. For example, in one embodiment, such a nucleic acid molecule is at least 250-300, 300-335, 339, 339-350, 350-400, 400-450, 467, 467-500, 500-550, or 550-600, 600-750, 762, 762-800, 800-900, 918, 918-1000, 1000-1200, 1236, 1275, 1275-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2400, 2400-2800, 2800-2900, 2962, or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or, the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a complement thereof.

On page 4, please amend the paragraph beginning at line 27 as follows:

In other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2 or 8, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 or 3, or SEQ ID NO:7 or 9, respectively, under stringent conditions.

On page 5, please amend the paragraph beginning at line 6 as follows:

Another aspect of this invention features isolated or recombinant CARK proteins and polypeptides. In one embodiment, the isolated protein, preferably a CARK protein, includes at least one ankyrin repeat domain, and preferably two, three, four, five, six, seven, eight, or, most preferably, nine or more ankyrin repeat domains. In another embodiment, the isolated protein, preferably a CARK protein, includes at least one protein kinase domain. In a preferred embodiment, the protein, preferably a CARK protein, includes at least one ankyrin repeat domain and preferably two, three, four, five, six, seven, eight, or, most preferably, nine or more ankyrin repeat domains, and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the amino acid sequence of SEQ ID NO:2 or 8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In another preferred embodiment, the protein, preferably a CARK protein, includes at least one protein kinase domain and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the amino acid sequence of SEQ ID NO:2 or 8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In another preferred embodiment, the protein, preferably a CARK protein, includes at least one LXCXE motif and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the amino acid sequence of SEQ ID NO:2 or 8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In yet another preferred embodiment, the protein, preferably a CARK protein,

includes at least one ankyrin repeat domain and preferably two, three, four, five, six, seven, eight, or, most preferably, nine or more ankyrin repeat domains, at least one protein kinase domain, and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the amino acid sequence of SEQ ID NO:2 or 8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In a preferred embodiment, a CARK protein includes at least one or more of the following domains and/or motifs: an ankyrin repeat domain, a kinase domain or a LXCXE motif, and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 98% or more homologous to the amino acid sequence of SEQ ID NO:2 or 8, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]].

On pages 6 and 7, please amend the paragraph beginning at line 37 of page 6 as follows:

In another embodiment, the invention features fragments of the protein having the amino acid sequence of SEQ ID NO:2 or 8, wherein the fragment comprises at least 15 amino acids (*e.g.*, contiguous amino acids) of the amino acid sequence of SEQ ID NO:2 or 8 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number PTA-1530[[_____]]. In one embodiment, the protein comprises amino acid residues 463 to 716 of SEQ ID NO:2 or 8. In another embodiment, the invention comprises amino acid residues 411-415 of SEQ ID NO:2 or 8. In yet another embodiment, the protein, preferably a CARK protein, has the amino acid sequence of SEQ ID NO:2 or 8.

On pages 13 and 14, please amend the paragraphs beginning at line 6 of page 13 as follows:

For example, the family of CARK proteins comprise at least one, and preferably two, three, four, five, six, seven, eight, or most preferably, nine or more ankyrin repeat domains. As used herein, the term "ankyrin repeat domain" includes a protein domain involved in protein:protein interactions, having an amino acid sequence of about 20-40 amino acid residues and having a bit score for the alignment of the sequence to the ankyrin repeat domain (HMM) of at least 1. Preferably, an ankyrin repeat domain includes at least about 25-40, more preferably about 25-35 amino acid residues, or most preferably about 30-35 amino acids and has a bit score

for the alignment of the sequence to the ankyrin repeat domain (HMM) of at least 3, 5, 10, 20, 30, 40, 50, or greater. The ankyrin repeat domain (HMM) has been assigned the PFAM Accession PF00023 ([[http://]]genome.wustl.edu/Pfam/.html). Ankyrin repeats are described in, for example, Otto E. *et al.* (1991) *J. Biol. Chem.* 114:241-253, Hatada E.N. *et al.* (1992) *PNAS USA* 89:2489-2493, and Blank V.P. *et al.* (1992) *Trends Genet.* 8:144-149, the contents of which are incorporated herein by reference.

To identify the presence of an ankyrin repeat domain in a CARK protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of HMMs (*e.g.*, the Pfam database, release 2.1) using the default parameters ([[http://]]www.sanger.ac.uk/Software/Pfam/HMM_search). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (*e.g.*, to 8 bits). A description of the Pfam database can be found in Sonhammer *et al.* (1997) *Proteins* 28(3)405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.*(1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.*(1987) *Proc. Natl. Acad. Sci. USA* 84:4355-4358; Krogh *et al.*(1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.*(1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference. A search was performed against the HMM database resulting in the identification of nine ankyrin repeat domains in the amino acid sequence of human CARK (SEQ ID NO:2) at about residues 66-99, 100-132, 133-165, 168-198, 199-233, 234-268, 269-302, 306-338, and 339-371 of SEQ ID NO:2. The results of the search are set forth in Figure 4. Nine ankyrin repeat domains were also identified in the amino acid sequence of rat CARK (SEQ ID NO:8) at about residues 66-99, 100-132, 133-165, 168-198, 199-233, 234-264, 269-302, 306-338, and 339-371 of SEQ ID NO:8. The results of the search are set forth in Figure 6.

On page 14, please amend the paragraph beginning at line 10 as follows:

In another embodiment, a CARK of the present invention is identified based on the presence of a "protein kinase domain" in the protein or corresponding nucleic acid molecule. As used herein, the term " protein kinase domain " includes a protein domain having an amino acid sequence of about 200-400 amino acid residues and having a bit score for the alignment of the

sequence to the protein kinase domain (HMM) of at least 200. Preferably, a protein kinase domain includes at least about 200-300, and more preferably about 250-300 amino acid residues, and has a bit score for the alignment of the sequence to the protein kinase domain (HMM) of at least 210, 220, 230, 250, 300 or greater. The protein kinase domain (HMM) has been assigned the PFAM Accession PF00069 ([[http://]]genome.wustl.edu/Pfam/.html).

On page 16, please amend the paragraph beginning at line 19 as follows:

The nucleotide sequence of the isolated human CARK cDNA and the predicted amino acid sequence of the human CARK polypeptide are shown in Figure 1 and in SEQ ID NOs:1 and 2, respectively. A plasmid containing the nucleotide sequence encoding human CARK was deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on March 21, 2000[[_____]] and assigned Accession Number PTA-1530[[_____]]. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

On pages 16 and 17, please amend the paragraph beginning at line 31 of page 16 as follows:

The nucleotide sequence of the isolated rat CARK cDNA and the predicted amino acid sequence of the rat CARK polypeptide are shown in Figure 5 and in SEQ ID NOs:7 and 8, respectively. A plasmid containing the nucleotide sequence encoding rat CARK was deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on March 21, 2000[[_____]] and assigned Accession Number PTA-1530[[_____]]. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.

On pages 17 and 18, please amend the paragraphs beginning at line 34 of page 17 as follows:

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], as a hybridization probe, CARK nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]] can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]].

On pages 18 and 19, please amend the paragraphs beginning at line 33 of page 18 as follows:

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, 3,

7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 82%, 85%, 90%, 95%, 98% or more homologous to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or the entire length of the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a portion of any of these nucleotide sequences.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a CARK protein, *e.g.*, a biologically active portion of a CARK protein. The nucleotide sequence determined from the cloning of the CARK gene allows for the generation of probes and primers designed for use in identifying and/or cloning other CARK family members, as well as CARK homologues from other species. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], of an anti-sense sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In an exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is greater than 250-300, 300-350, 350-400, 400-450, 467, 467-500, 500-550, or 550-600, 600-800, 800-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2400, 2400-2800, 2800-2900, 2962 or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]].

On page 20, please amend the paragraphs beginning at line 7 as follows:

A nucleic acid fragment encoding a "biologically active portion of a CARK protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], which encodes a polypeptide having a CARK biological activity (the biological activities of the CARK proteins are described herein), expressing the encoded portion of the CARK protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the CARK protein.

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], due to degeneracy of the genetic code and thus encode the same CARK proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2 or 8.

In addition to the CARK nucleotide sequences shown in SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the CARK proteins may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the CARK genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding a CARK protein, preferably a mammalian CARK protein, and can further include non-coding regulatory sequences, and introns.

On page 21, please amend the paragraph beginning at line 14 as follows:

Moreover, nucleic acid molecules encoding other CARK family members and, thus, which have a nucleotide sequence which differs from the CARK sequences of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as

Accession Number PTA-1530[[_____]] are intended to be within the scope of the invention. For example, another CARK cDNA can be identified based on the nucleotide sequence of human or rat CARK. Moreover, nucleic acid molecules encoding CARK proteins from different species, and which, thus, have a nucleotide sequence which differs from the CARK sequences of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]] are intended to be within the scope of the invention. For example, a mouse CARK cDNA can be identified based on the nucleotide sequence of a human or rat CARK.

On page 21, please amend the paragraph beginning at line 32 as follows:

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 350, 400, 450, 467, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1500, 2000, 2500, or 2962 or more nucleotides in length.

On page 23, please amend the paragraph beginning at line 8 as follows:

In addition to naturally-occurring allelic variants of the CARK sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], thereby leading to changes in the amino acid sequence of the encoded CARK proteins, without altering the functional ability of the CARK proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of CARK (*e.g.*, the sequence of SEQ ID NO:2 or 8) without altering the biological activity, whereas an

"essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the CARK proteins of the present invention, *e.g.*, those present in the active site of the protein kinase domain, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the CARK proteins of the present invention and other ankyrin repeat containing kinases are not likely to be amenable to alteration.

On pages 23 and 24, please amend the paragraph beginning at line 32 of page 23 as follows:

An isolated nucleic acid molecule encoding a CARK protein homologous to the protein of SEQ ID NO:2 or 8 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]] by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a CARK protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a CARK coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for CARK biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the

plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

On pages 26 and 27, please amend the paragraph beginning at line 27 of page 26 as follows:

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave CARK mRNA transcripts to thereby inhibit translation of CARK mRNA. A ribozyme having specificity for a CARK-encoding nucleic acid can be designed based upon the nucleotide sequence of a CARK cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 3, 7, or 9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]]). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a CARK-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, CARK mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

On pages 30 and 31, please amend the paragraphs beginning at line 32 of page 30 as follows:

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at [[http://]]www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at [[http://]]www.gcg.com), using a NWSgapdna.CMP matrix and a gap

weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (Comput Appl Biosci, 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to CARK nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to CARK protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See [[http://]]www.ncbi.nlm.nih.gov.

On page 44, please amend the paragraph beginning at line 1 as follows:

A transgenic animal of the invention can be created by introducing a CARK-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The CARK cDNA sequence of SEQ ID NO:1 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human CARK gene, such as a mouse or rat CARK gene (*e.g.*, SEQ ID NO:7), can be used as a transgene. Alternatively, a CARK gene homologue, such as another CARK family member, can be isolated based on hybridization to the CARK cDNA sequences of SEQ ID NO:1, 3, 7, or 9, or the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]] (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a CARK transgene to direct

expression of a CARK protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a CARK transgene in its genome and/or expression of CARK mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a CARK protein can further be bred to other transgenic animals carrying other transgenes.

On page 63, please amend the paragraph beginning at line 25 as follows:

An exemplary method for detecting the presence or absence of CARK protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting CARK protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes CARK protein such that the presence of CARK protein or nucleic acid is detected in the biological sample. A preferred agent for detecting CARK mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to CARK mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length CARK nucleic acid, such as the nucleic acid of SEQ ID NO:1, 3, 7, or 9, or the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530[[_____]], or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to CARK mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.